New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk

Published in final edited form as:
Nat Genet. 2010 February ; 42(2): 105–116. doi:10.1038/ng.520.

New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk

Josée Dupuis[1,2,*], **Claudia Langenberg**[3,*], **Inga Prokopenko**[4,5,*], **Richa Saxena**[6,7,*], **Nicole Soranzo**[8,9,*], **Anne U Jackson**[10], **Eleanor Wheeler**[11], **Nicole L Glazer**[12], **Nabila Bouatia-Naji**[13], **Anna L Gloyn**[4], **Cecilia M Lindgren**[4,5], **Reedik Mägi**[4,5], **Andrew P Morris**[5], **Joshua Randall**[5], **Toby Johnson**[14,15,16], **Paul Elliott**[17], **Denis Rybin**[18], **Gudmar Thorleifsson**[19], **Valgerdur Steinthorsdottir**[19], **Peter Henneman**[20], **Harald Grallert**[21], **Abbas Dehghan**[22], **Jouke Jan Hottenga**[23], **Christopher S Franklin**[24], **Pau Navarro**[25], **Kijoung Song**[26], **Anuj Goel**[5,27], **John R B Perry**[28], **Josephine M Egan**[29], **Taina Lajunen**[30], **Niels Grarup**[31], **Thomas Sparsø**[31], **Alex Doney**[32], **Benjamin F Voight**[6,7], **Heather M Stringham**[10], **Man Li**[33], **Stavroula Kanoni**[34], **Peter Shrader**[35], **Christine Cavalcanti-Proença**[13], **Meena Kumari**[36], **Lu Qi**[37], **Nicholas J Timpson**[38], **Christian Gieger**[21], **Carina Zabena**[39], **Ghislain Rocheleau**[40,41], **Erik Ingelsson**[42,43], **Ping An**[44], **Jeffrey O'Connell**[45], **Jian'an Luan**[3], **Amanda Elliott**[6,7], **Steven A McCarroll**[6,7], **Felicity Payne**[11], **Rosa Maria Roccasecca**[11], **François Pattou**[46], **Praveen Sethupathy**[47], **Kristin Ardlie**[48], **Yavuz Ariyurek**[49], **Beverley Balkau**[50], **Philip Barter**[51], **John P Beilby**[52,53], **Yoav Ben-Shlomo**[54], **Rafn Benediktsson**[55,56], **Amanda J Bennett**[4], **Sven Bergmann**[14,15], **Murielle Bochud**[15], **Eric Boerwinkle**[57], **Amélie Bonnefond**[13], **Lori L Bonnycastle**[47], **Knut Borch-Johnsen**[58,59], **Yvonne Böttcher**[60], **Eric Brunner**[36], **Suzannah J Bumpstead**[8], **Guillaume Charpentier**[61], **Yii-Der Ida Chen**[62], **Peter Chines**[47], **Robert Clarke**[63], **Lachlan J M Coin**[17], **Matthew N Cooper**[64], **Marilyn Cornelis**[37], **Gabe Crawford**[6], **Laura Crisponi**[65], **Ian N M Day**[38], **Eco de Geus**[23], **Jerome Delplanque**[13], **Christian Dina**[13], **Michael R Erdos**[47], **Annette C Fedson**[64,66], **Antje Fischer-Rosinsky**[67,68], **Nita G Forouhi**[3], **Caroline S Fox**[2,69], **Rune Frants**[70], **Maria Grazia Franzosi**[71], **Pilar Galan**[72], **Mark O Goodarzi**[62], **Jürgen Graessler**[73], **Christopher J Groves**[4], **Scott Grundy**[74], **Rhian Gwilliam**[8], **Ulf Gyllensten**[75], **Samy Hadjadj**[76], **Göran Hallmans**[77], **Naomi Hammond**[8], **Xijing Han**[10], **Anna-Liisa Hartikainen**[78], **Neelam Hassanali**[4], **Caroline Hayward**[25], **Simon C Heath**[79], **Serge Hercberg**[80], **Christian Herder**[81], **Andrew A Hicks**[82], **David R Hillman**[66,83], **Aroon D Hingorani**[36], **Albert Hofman**[22], **Jennie Hui**[52,84], **Joe Hung**[85,86], **Bo Isomaa**[87,88], **Paul R V Johnson**[4,89], **Torben Jørgensen**[90,91], **Antti Jula**[92], **Marika Kaakinen**[93], **Jaakko Kaprio**[94,95,96], **Y Antero Kesaniemi**[97], **Mika Kivimaki**[36], **Beatrice Knight**[98], **Seppo Koskinen**[99], **Peter Kovacs**[100], **Kirsten Ohm Kyvik**[101], **G Mark Lathrop**[79], **Debbie A Lawlor**[38], **Olivier Le Bacquer**[13], **Cécile Lecoeur**[13], **Yun Li**[10], **Valeriya Lyssenko**[102], **Robert Mahley**[103], **Massimo Mangino**[9], **Alisa K Manning**[1], **María Teresa Martínez-Larrad**[39], **Jarred B McAteer**[6,104,105], **Laura J McCulloch**[4], **Ruth McPherson**[106], **Christa Meisinger**[21], **David Melzer**[28], **David Meyre**[13], **Braxton D Mitchell**[45], **Mario A Morken**[47], **Sutapa Mukherjee**[66,83], **Silvia Naitza**[65],

Corresponding authors: **Michael Boehnke**, Department of Biostatistics and Center for Statistical Genetics, University of Michigan, 1420 Washington Heights, Ann Arbor, MI 48109 – USA, Tel. +1 734 936 1001, Fax. +1 734 615 8322, boehnke@umich.edu, **Mark I. McCarthy**, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ – UK, Tel. +44 (0) 1865 857298, Fax. +44 (0) 1865 857299, mark.mccarthy@drl.ox.ac.uk, **Jose C. Florez**, Diabetes Research Center (Diabetes Unit), and Center for Human Genetic Research, Simches Research Building – CPZN 5.250, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114 – USA, Tel. +1 617 643 3308, Fax. +1 617 643 6630, jcflorez@partners.org, **Inês Barroso**, Metabolic Disease Group, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SA, UK, Tel. +44 (0) 1223 495341, Fax. +44 (0) 1223 494919, ib1@sanger.ac.uk.
*These authors contributed equally
145See appendix for full list of authors

Narisu Narisu[47], **Matthew J Neville**[4,107], **Ben A Oostra**[108], **Marco Orrù**[65], **Ruth Pakyz**[45], **Colin N A Palmer**[109], **Giuseppe Paolisso**[110], **Cristian Pattaro**[82], **Daniel Pearson**[47], **John F Peden**[5,27], **Nancy L. Pedersen**[42], **Markus Perola**[96,111,112], **Andreas F H Pfeiffer**[67,68], **Irene Pichler**[82], **Ozren Polasek**[113], **Danielle Posthuma**[23,114], **Simon C Potter**[8], **Anneli Pouta**[115], **Michael A Province**[44], **Bruce M Psaty**[116,117], **Wolfgang Rathmann**[118], **Nigel W Rayner**[4,5], **Kenneth Rice**[119], **Samuli Ripatti**[96,111], **Fernando Rivadeneira**[22,120], **Michael Roden**[81,121], **Olov Rolandsson**[122], **Annelli Sandbaek**[123], **Manjinder Sandhu**[3,124], **Serena Sanna**[65], **Avan Aihie Sayer**[125], **Paul Scheet**[126], **Laura J Scott**[10], **Udo Seedorf**[127], **Stephen J Sharp**[3], **Beverley Shields**[98], **Gunnar Sigurðsson**[55,56], **Erik J G Sijbrands**[22,120], **Angela Silveira**[128], **Laila Simpson**[64,66], **Andrew Singleton**[129], **Nicholas L Smith**[130,131], **Ulla Sovio**[17], **Amy Swift**[47], **Holly Syddall**[125], **Ann-Christine Syvänen**[132], **Toshiko Tanaka**[133,134], **Barbara Thorand**[21], **Jean Tichet**[135], **Anke Tönjes**[60,136], **Tiinamaija Tuomi**[87,137], **André G Uitterlinden**[22,120], **Ko Willems van Dijk**[70,138], **Mandy van Hoek**[120], **Dhiraj Varma**[8], **Sophie Visvikis-Siest**[139], **Veronique Vitart**[25], **Nicole Vogelzangs**[140], **Gérard Waeber**[141], **Peter J Wagner**[96,111], **Andrew Walley**[142], **G Bragi Walters**[19], **Kim L Ward**[64,66], **Hugh Watkins**[5,27], **Michael N Weedon**[28], **Sarah H Wild**[24], **Gonneke Willemsen**[23], **Jaqueline C M Witteman**[22], **John W G Yarnell**[143], **Eleftheria Zeggini**[5,8], **Diana Zelenika**[79], **Björn Zethelius**[43,144], **Guangju Zhai**[9], **Jing Hua Zhao**[3], **M Carola Zillikens**[120], **DIAGRAM Consortium**[145], **GIANT Consortium**[145], **Global BPgen Consortium**[145], **Ingrid B Borecki**[44], **Ruth J F Loos**[3], **Pierre Meneton**[80], **Patrik K E Magnusson**[42], **David M Nathan**[104,105], **Gordon H Williams**[69,105], **Andrew T Hattersley**[98], **Kaisa Silander**[96,111], **Veikko Salomaa**[146], **George Davey Smith**[38], **Stefan R Bornstein**[73], **Peter Schwarz**[73], **Joachim Spranger**[67,68], **Fredrik Karpe**[4,107], **Alan R Shuldiner**[45], **Cyrus Cooper**[125], **George V Dedoussis**[34], **Manuel Serrano-Ríos**[39], **Andrew D Morris**[109], **Lars Lind**[132], **Lyle J Palmer**[64,66,84], **Frank B. Hu**[147,148], **Paul W Franks**[149], **Shah Ebrahim**[150], **Michael Marmot**[36], **W H Linda Kao**[33,151,152], **James S Pankow**[153], **Michael J Sampson**[154], **Johanna Kuusisto**[155], **Markku Laakso**[155], **Torben Hansen**[31,156], **Oluf Pedersen**[31,59,157], **Peter Paul Pramstaller**[82,158,159], **H Erich Wichmann**[21,160,161], **Thomas Illig**[21], **Igor Rudan**[24,162,163], **Alan F Wright**[25], **Michael Stumvoll**[60], **Harry Campbell**[24], **James F Wilson**[24], **Anders Hamsten**[128] **on behalf of Procardis consortium**, **Richard N Bergman**[164], **Thomas A Buchanan**[164,165], **Francis S Collins**[47], **Karen L Mohlke**[166], **Jaakko Tuomilehto**[94,167], **Timo T Valle**[167], **David Altshuler**[6,7,104,105], **Jerome I Rotter**[62], **David S Siscovick**[168], **Brenda W J H Penninx**[140], **Dorret Boomsma**[23], **Panos Deloukas**[8], **Timothy D Spector**[8,9], **Timothy M Frayling**[28], **Luigi Ferrucci**[169], **Augustine Kong**[19], **Unnur Thorsteinsdottir**[19,170], **Kari Stefansson**[19,170], **Cornelia M van Duijn**[22], **Yurii S Aulchenko**[22], **Antonio Cao**[65], **Angelo Scuteri**[65,171], **David Schlessinger**[47], **Manuela Uda**[65], **Aimo Ruokonen**[172], **Marjo-Riitta Jarvelin**[17,93,173], **Dawn M Waterworth**[26], **Peter Vollenweider**[141], **Leena Peltonen**[8,48,96,111,112], **Vincent Mooser**[26], **Goncalo R Abecasis**[10], **Nicholas J Wareham**[3], **Robert Sladek**[40,41], **Philippe Froguel**[13,142], **Richard M Watanabe**[164,174], **James B Meigs**[35,105], **Leif Groop**[102], **Michael Boehnke**[10], **Mark I McCarthy**[4,5,107], **Jose C Florez**[6,7,104,105], **Inês Barroso**[11], and **for the MAGIC investigators**

[1]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA [2]National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts 01702, USA [3]MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK [4]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford OX3 7LJ, UK [5]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK [6]Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts 02142, USA [7]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA [8]Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK [9]Twin Research & Genetic Epidemiology Department, King's College London, St Thomas' Hospital Campus, Lambeth Palace Rd, London SE1 7EH, UK [10]Center for Statistical Genetics, Department of Biostatistics,

University of Michigan School of Public Health, Ann Arbor, Michigan 48109, USA [11]Metabolic Disease Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK [12]Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington, USA [13]CNRS-UMR8090, Pasteur Institute, Lille 2-Droit et Santé University, F-59000 Lille, France [14]Department of Medical Genetics, University of Lausanne, 1005 Lausanne, Switzerland [15]University Institute of Social and Preventative Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, 1005 Lausanne, Switzerland [16]Swiss Institute of Bioinformatics, Switzerland [17]Department of Epidemiology and Public Health, Imperial College of London, Faculty of Medicine, Norfolk Place, London W2 1PG, UK [18]Boston University Data Coordinating Center, Boston, Massachusetts 02118, USA [19]deCODE Genetics, 101 Reykjavik, Iceland [20]Department of Human Genetics, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands [21]Institute of Epidemiology, Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, 85764 Neuherberg, Germany [22]Department of Epidemiology, Erasmus MC Rotterdam, 3000 CA, The Netherlands [23]Department of Biological Psychology, VU, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands [24]Centre for Population Health Sciences, University of Edinburgh, Edinburgh EH8 9AG, UK [25]MRC Human Genetics Unit, IGMM, Edinburgh EH4 2XU, UK [26]Division of Genetics, R&D, Glaxo SmithKline, King of Prussia, Pennsylvania 19406, USA [27]Department of Cardiovascular Medicine, University of Oxford, Oxford OX3 9DU, UK [28]Genetics of Complex Traits, Institute of Biomedical and Clinical Sciences, Peninsula College of Medicine and Dentistry, University of Exeter EX1 2LU, UK [29]Laboratory of Clinical Investigation, National Institute of Aging, Baltimore, Maryland 21250, USA [30]Unit for Child and Adolescent Health and Welfare, National Institute for Health and Welfare, Biocenter Oulu, University of Oulu, 90014 Oulu, Finland [31]Hagedorn Research Institute, 2820 Gentofte, Denmark [32]Department of Medicine & Therapeutics, Level 7, Ninewells Hospital & Medical School, Dundee DD1 9SY, UK [33]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland 21287, USA [34]Department of Nutrition - Dietetics, Harokopio University, 17671 Athens, Greece [35]General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, USA [36]Department of Epidemiology and Public Health, University College London, UK [37]Depts. of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA [38]MRC Centre for Causal Analyses in Translational Epidemiology, University of Bristol, Bristol BS8 2PR, UK [39]Fundación para la Investigación Biomédica del Hospital Clínico San Carlos, Madrid, Spain [40]Departments of Medicine and Human Genetics, McGill University, Montreal, Canada [41]Genome Quebec Innovation Centre, Montreal H3A 1A4, Canada [42]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden [43]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden [44]Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St. Louis, Missouri, USA [45]Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA [46]INSERM U859, Universite de Lille-Nord de France, F-59000 Lille, France [47]Genome Technology Branch, National Human Genome Research Institute, Bethesda, Maryland 20892, USA [48]The Broad Institute, Cambridge, Massachusetts 02141, USA [49]Leiden Genome Technology Center, Leiden University Medical Center, 2300 RC Leiden, The Netherlands [50]INSERM U780-IFR69, Paris Sud University, F-94807 Villejuif, France [51]The Heart Research Institute, Sydney, New South Wales, Australia [52]PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, NEDLANDS WA 6009, Australia [53]School of Surgery and Pathology, University of Western Australia, Nedlands WA 6009, Australia [54]Department of Social Medicine, University of Bristol, Bristol BS8 2PR, UK [55]Landspitali University Hospital, 101 Reykjavik, Iceland [56]Icelandic Heart Association, 201 Kopavogur, Iceland [57]The Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas 77030, USA [58]Steno Diabetes Center, DK-2820 Gentofte, Copenhagen, Denmark [59]Faculty of

Health Science, University of Aarhus, Aarhus DK-8000, Denmark [60]Department of Medicine, University of Leipzig, Liebigstr. 18, 04103 Leipzig, Germany [61]Endocrinology-Diabetology Unit, Corbeil-Essonnes Hospital, Essonnes, F-91108 France [62]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA [63]Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford OX3 7LF, UK [64]Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Perth, Australia [65]Istituto di Neurogenetica e Neurofarmacologia (INN), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Monserrato, Cagliari 09042, Italy [66]Western Australian Sleep Disorders Research Institute, Queen Elizabeth Medical Centre II, Perth, Australia [67]Department of Endocrinology, Diabetes and Nutrition, Charite-Universitaetsmedizin Berlin, Berlin, Germany [68]Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany [69]Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA [70]Department of Human Genetics, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands [71]Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy [72]U557 Institut National de la Santé et de la Recherche Médicale, U1125 Institut National de la Recherche Agronomique, Université Paris 13, 74 rue Marcel Cachin, 93017 Bobigny Cedex, France [73]Department of Medicine III, Division Prevention and Care of Diabetes, University of Dresden, 01307 Dresden [74]Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas, USA [75]Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, S-751 85 Uppsala, Sweden [76]CHU de Poitiers, Endocrinologie Diabetologie, CIC INSERM 0802, INSERM U927, Université de Poitiers, UFR, Médecine Pharmacie, Poitiers, France [77]Department of Public Health & Clinical Medicine, Section for Nutritional Research, Umeå University, Umeå, Sweden [78]Department of Clinical Sciences, Obstetrics and Gynecology, University of Oulu, Box 5000, Fin-90014 University of Oulu, Finland [79]Centre National de Génotypage/IG/CEA, 2 rue Gaston Crémieux CP 5721, 91057 Evry Cedex, France [80]U872 Institut National de la Santé et de la Recherche Médicale, Faculté de Médecine Paris Descartes, 15 rue de l'Ecole de Médecine, 75270 Paris Cedex, France [81]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany [82]Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso 1, 39100 Bolzano, Italy, Affiliated Institute of the University Lübeck, Germany [83]Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Perth, Australia [84]Busselton Population Medical Research Foundation, Sir Charles Gairdner Hospital, Perth, Australia [85]Heart Institute of Western Australia, Sir Charles Gairdner Hospital, Nedlands WA 6009, Australia [86]School of Medicine and Pharmacology, University of Western Australia, Nedlands, WA 6009, Australia [87]Folkhalsan Research Centre, Helsinki, Finland [88]Malmska Municipal Health Care Center and Hospital, Jakobstad, Finland [89]Nuffield Department of Surgery, University of Oxford, Oxford OX3 9DU, UK [90]Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark [91]Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark [92]National Institute for Health and Welfare, Unit of Population Studies, Turku, Finland [93]Institute of Health Sciences and Biocenter Oulu, Box 5000, Fin-90014 University of Oulu, Finland [94]Department of Public Health, Faculty of Medicine, P.O. Box 41 (Mannerheimintie 172), University of Helsinki, 00014 Helsinki, Finland [95]National Institute for Health and Welfare, Unit for Child and Adolescent Mental Health, Helsinki, Finland [96]Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland [97]Department of Internal Medicine and Biocenter Oulu, Oulu, Finland [98]Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter EX2 5DW, UK [99]National Institute for Health and Welfare, Unit of Living Conditions, Health and Wellbeing, Helsinki, Finland [100]Interdisciplinary Centre for Clinical Research, University of Leipzig, Inselstr. 22, 04103 Leipzig, Germany [101]The Danish Twin Registry, Epidemiology, Institute of Public Health, University of Southern Denmark, J.B. Winsløws

Vej 9B, 5000 Odense, Denmark [102]Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, University Hospital Malmo, Malmo, Sweden [103]Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, California, USA [104]Diabetes Research Center (Diabetes Unit), Massachusetts General Hospital, Boston, Massachusetts 02114, USA [105]Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA [106]Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada [107]Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford OX3 7LJ, UK [108]Department of Clinical Genetics, Erasmus MC Rotterdam, 3000 CA, The Netherlands [109]Biomedical Research Institute, University of Dundee, Ninewells Hospital & Medical School, Dundee DD1 9SY, UK [110]Department of Geriatric Medicine and Metabolic Disease, Second University of Naples, Naples, Italy. [111]National Institute for Health and Welfare, Unit of Public Health Genomics, Helsinki, Finland [112]Department of Medical Genetics, University of Helsinki, Helsinki, Finland [113]Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija Stampar School of Public Health, Medical School, University of Zagreb, Rockefellerova 4, 10000 Zagreb, Croatia [114]Department of Clinical Genetics, VUMC, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands [115]Department of Obstetrics and Gynaecology, Oulu University Hospital, Oulu, Finland [116]Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, Washington, USA [117]Group Health Center for Health Studies, Seattle, Washington, USA [118]Institute of Biometrics and Epidemiology, German Diabetes Centre, Leibniz Centre at Heinrich Heine University Düsseldorf, Düsseldorf, Germany [119]Department of Biostatistics, University of Washington, Seattle, Washington 98195, USA [120]Department of Internal Medicine, Erasmus MC Rotterdam, 3000 CA, The Netherlands [121]Department of Medicine/Metabolic Diseases, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany [122]Department of Public Health & Clinical Medicine, Section for Family Medicine, Umeå University Hospital, Umeå, Sweden [123]School of Public Health, Department of General Practice, University of Aarhus, Aarhus DK-8000, Denmark [124]Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK [125]MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK [126]Department of Epidemiology, University of Texas, M.D. Anderson Cancer Center, Houston, Texas, 77030, USA [127]Leibniz-Institut für Arteriosklerosеforschung an der Universität Münster,Münster, Germany [128]Atherosclerosis Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden [129]Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland 20892, USA [130]Department of Epidemiology, University of Washington, Seattle, Washington 98195, USA [131]Seattle Epidemiologic Research and Information Center, Department of Veterans Affairs Office of Research and Development, Seattle, Washington, USA [132]Department of Medical Sciences, Uppsala University, Uppsala, Sweden [133]Medstar Research Institute, Baltimore, Maryland 21250, USA [134]Clinical Research Branch, National Institute on Aging, Baltimore, Maryland 21250, USA [135]Institut interrégional pour la santé (IRSA), F-37521 La Riche, France [136]Coordination Centre for Clinical Trials, University of Leipzig, Härtelstr. 16-18, 04103 Leipzig, Germany [137]Department of Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland [138]Department of Internal Medicine, Leiden University Medical Centre, 2300 RC Leiden, The Netherlands [139]Research Unit, Cardiovascular Genetics, Nancy University Henri Poincaré, Nancy, France [140]EMGO Institute/Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands [141]Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland [142]Genomic Medicine, Imperial College London, Hammersmith Hospital, W12 0NN, London, UK [143]Epidemiology & Public Health, Queen's University Belfast, Belfast BT12 6BJ, UK [144]Medical Products Agency, Uppsala, Sweden [146]National Institute for Health and Welfare, Unit of Chronic Disease Epidemiology and Prevention, Helsinki, Finland [147]Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA [148]Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston,

Massachusetts, USA [149]Genetic Epidemiology & Clinical Research Group, Department of Public Health & Clinical Medicine, Section for Medicine, Umeå University Hospital, Umeå, Sweden [150]London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK [151]Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland 21287, USA [152]The Welch Center for Prevention, Epidemiology, and Clinical Research, School of Medicine and Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland 21287, USA [153]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota 55454, USA [154]Department of Endocrinology and Diabetes, Norfolk and Norwich University Hospital NHS Trust, Norwich, NR1 7UY, UK [155]Department of Medicine, University of Kuopio and Kuopio University Hospital, Kuopio 70210, Finland [156]Faculty of Health Science, University of Southern Denmark, Odense, Denmark [157]Institute of Biomedical Science, Faculty of Health Science, University of Copenhagen, Denmark [158]Department of Neurology, General Central Hospital, 39100 Bolzano, Italy [159]Department of Neurology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany [160]Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany [161]Klinikum Grosshadern, Munich, Germany [162]School of Medicine, University of Split, Soltanska 2, 21000 Split, Croatia [163]Gen-Info Ltd, Ruzmarinka 17, 10000 Zagreb, Croatia [164]Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA [165]Department of Medicine, Division of Endocrinology, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA [166]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA [167]National Institute for Health and Welfare, Unit of Diabetes Prevention, Helsinki, Finland [168]Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington, USA [169]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, NIH, Baltimore, Maryland, USA [170]Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland [171]Lab of Cardiovascular Sciences, National Institute on Aging, NIH, Baltimore, Maryland, USA [172]Department of Clinical Sciences/Clinical Chemistry, University of Oulu, Box 5000, Fin-90014 University of Oulu, Finland [173]National Institute of Health and Welfare, Aapistie 1, P.O. Box 310, Fin-90101 Oulu, Finland [174]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, 90033, USA

Abstract

Circulating glucose levels are tightly regulated. To identify novel glycemic loci, we performed meta-analyses of 21 genome-wide associations studies informative for fasting glucose (FG), fasting insulin (FI) and indices of β-cell function (HOMA-B) and insulin resistance (HOMA-IR) in up to 46,186 non-diabetic participants. Follow-up of 25 loci in up to 76,558 additional subjects identified 16 loci associated with FG/HOMA-B and two associated with FI/HOMA-IR. These include nine new FG loci (in or near *ADCY5*, *MADD*, *ADRA2A*, *CRY2*, *FADS1*, *GLIS3*, *SLC2A2*, *PROX1* and *FAM148B*) and one influencing FI/HOMA-IR (near *IGF1*). We also demonstrated association of *ADCY5*, *PROX1*, *GCK*, *GCKR* and *DGKB/TMEM195* with type 2 diabetes (T2D). Within these loci, likely biological candidate genes influence signal transduction, cell proliferation, development, glucose-sensing and circadian regulation. Our results demonstrate that genetic studies of glycemic traits can identify T2D risk loci, as well as loci that elevate FG modestly, but do not cause overt diabetes.

Impaired β-cell function and insulin resistance are key determinants of type 2 diabetes (T2D). Hyperglycemia in the fasting state is one of the criteria that define the disease1, can predict hard clinical endpoints in non-diabetic individuals2,3 and, when corrected in patients with T2D, may help prevent microvascular4,5 and long-term macrovascular6,7 complications. To date, there are nearly 20 published loci reproducibly associated with

T2D[8], with most of them also associated with decreased insulin secretion[9] due to defective β-cell function or mass. Association studies for diabetes-related quantitative traits in non-diabetic participants have also identified loci influencing fasting glucose (FG) levels, whose effects appear to be mediated by impairment of the glucose-sensing machinery in β-cells[10–17].

We recently formed the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) to conduct large-scale meta-analyses of genome-wide data for continuous diabetes-related traits in non-diabetic participants[15]. We aimed to identify additional loci that influence glycemic traits in persons free of diabetes, and investigate their impact on related metabolic phenotypes. We were also interested in understanding variation in the physiological range and evaluating the extent to which the same variants influence pathological FG variation and T2D risk. The initial MAGIC collaboration identified the FG/T2D-associated locus *MTNR1B*[15], which was also reported by others[16,17]; this finding demonstrated that studies of continuous glycemic phenotypes in non-diabetic individuals can complement the genetic analyses of diabetes as a dichotomous trait, and improve our understanding of the mechanisms involved in β-cell function and glucose homeostasis. Here, we extend our previous approach by performing meta-analyses of ~2.5M directly genotyped or imputed autosomal SNPs from 21 genome-wide association studies (GWAS). These 21 cohorts include up to 46,186 non-diabetic participants of European descent informative for FG, and 20 GWAS including up to 38,238 non-diabetic individuals informative for fasting insulin (FI), as well as the surrogate estimates of β-cell function (HOMA-B) and insulin resistance (HOMA-IR) derived from fasting variables by homeostasis model assessment[18]. Follow-up of 25 lead SNPs in up to 76,558 additional individuals of European ancestry identified nine novel genome-wide significant associations (empirically determined as $P<5\times10^{-8}$)[19] with FG and one with FI/HOMA-IR. Five of these novel loci also demonstrated genome-wide significant evidence for association between the glucose-raising allele and T2D risk in up to 40,655 cases and 87,022 non-diabetic controls.

The wealth of novel FG and HOMA-B loci contrast with the sole FI/HOMA-IR novel finding and suggests a different genetic architecture for β-cell function and insulin resistance. Furthermore, our data support the hypothesis that not all loci that influence glycemia within the physiological range are also associated with pathological levels of glucose and T2D risk.

RESULTS

Genome wide association meta-analysis of glycemic traits (Stage 1)

We conducted a two-stage association study in individuals of European descent (Online Methods, Supplementary Figure 1, Supplementary Tables 1a and b). Because we sought to identify variants that influence FG in the normal population, hyperglycemia in the diabetic range exerts deleterious effects on β-cell function[20,21], and treatment can confound glucose and insulin measurements, we excluded individuals with known diabetes, on anti-diabetic treatment, or with FG ≥7 mmol/L. We combined data from 21 Stage 1 discovery GWAS for FG (N=46,186) and 20 GWAS for FI (N=38,238), HOMA-B (N=36,466) and HOMA-IR (N=37,037), and analyzed associations for ~2.5M autosomal SNPs directly genotyped and imputed[22,23] from HapMap CEU sample data assuming an additive genetic effect for each of the four traits.

Inverse variance weighted meta-analyses revealed 12 independent loci associated with FG and/or HOMA-B at genome-wide significance levels (Table 1, Supplementary Table 2, Supplementary Figure 2a–b). These included five novel associations for loci in or near *ADCY5, MADD, ADRA2A, CRY2* and *FADS1* (Table 1, Figure 1a–j); four previously

reported FG-associated loci in or near *GCK*, *GCKR*, *G6PC2*, and *MTNR1B*; the recently reported *DGKB/TMEM195*24; and two loci in T2D susceptibility genes *TCF7L2* (rs4506565, r^2=0.92 with the previously reported SNP rs7903146) and *SLC30A8* (rs11558471, r^2=0.96 with the previously reported SNP rs13266634). Seven additional loci had reproducible evidence for association with FG and/or HOMA-B across studies at the arbitrary summary threshold of $P<2\times10^{-5}$ chosen to prioritize SNPs for follow-up (Table 1, Supplementary Table 2). After excluding SNPs within the four previously genome-wide significant FG loci *GCK*, *GCKR*, *G6PC2* and *MTNR1B,* we still observed an excess of small *P*-values compared to a distribution expected under the null hypothesis (Figure 2a–b), suggesting that some of these additional loci are likely to represent novel FG and/or HOMA-B loci that merit additional investigation.

Stage 1 analyses of FI and HOMA-IR revealed no loci that reached genome-wide significance, but there were six loci with consistent evidence for association across study samples at $P<2\times10^{-5}$ (Table 1, Supplementary Table 2, Supplementary Figure 2c–d). Comparison of the observed *P*-values with the distribution expected under the null hypothesis demonstrated an excess of small *P*-values which warrant further investigation (Figure 2c–d).

Replication studies (Stage 2) and global (Stage 1 + Stage 2) meta-analysis for 25 loci

We carried forward to Stage 2 all independent loci with association with any of the four traits at $P<2\times10^{-5}$, except for SNPs in the known T2D genes *TCF7L2* and *SLC30A8* for which no further validation was sought (Table 1, Supplementary Table 2). We also included the nominally associated top SNP from a strong biological candidate (*IRS1*, $P=10^{-4}$ for HOMA-IR) and a locus with *P* values that approached genome-wide significance in several Stage 1 discovery cohorts (*PLXDC2/NEBL*), even though their overall Stage 1 *P*-values were $>2\times10^{-5}$ (Table 1, Supplementary Table 2). In total, 25 loci were chosen for replication.

We directly genotyped 25 variants in 26 additional Stage 2 studies with up to 63,850 non-diabetic participants of European ancestry for FG, and 25 studies and up to 52,892 participants for FI, HOMA-IR and HOMA-B (Supplementary Table 1b, Online Methods). We also obtained *in silico* replication data for 12,708 additional individuals from seven studies for FG (9,372 participants and five studies for FI, HOMA-IR and HOMA-B), for a total of up to 76,558 individuals for FG and 62,264 for FI, HOMA-IR and HOMA-B in Stage 2 association analyses.

Our combined Stage 1 and 2 meta-analysis, including a total of up to 122,743 participants for FG (98,372 for FI, HOMA-IR and HOMA-B) established genome-wide significant associations for nine novel loci for FG and/or HOMA-B (*ADCY5*, *MADD*, *CRY2*, *ADRA2A*, *FADS1*, *PROX1*, *SLC2A2*, *GLIS3*, *FAM148B*) and one for FI and HOMA-IR (*IGF1*) (Table 1 and Figure 1a–j). We hereby replicate the recently reported loci *DGKB/TMEM195* (FG)24 and *GCKR* (FG, FI and HOMA-IR)11،12،25 at levels that exceed genome-wide significance. Loci that had previously achieved genome-wide significant associations with FG (*G6PC2*, *MTNR1B* and *GCK*) were also confirmed (Table 1).

We further conducted a global meta-analysis of cohort results adjusted for body mass index (BMI), to test whether these diabetes-related quantitative trait associations may be mediated by associations with adiposity. The adjustment for BMI did not materially affect the strength of the associations with any of the traits (data not shown).

Effect size estimates for genome-wide significant loci

We restricted our effect size estimates (Table 2, Supplementary Table 2) to the Stage 2 replication samples (up to N=76,558) to avoid inflation introduced by the discovery cohorts ("winner's curse"26). The previously identified loci *G6PC2*, *MTNR1B* and *GCK* showed the largest effects on FG (0.075, 0.067 and 0.062 mmol/L per allele, respectively), with the remaining loci showing smaller effects (0.008 to 0.030 mmol/L per allele, Table 2). The proportion of variance in FG explained by the 14 FG loci with replication data (i.e. all FG loci except for *TCF7L2* and *SLC30A8*) ranged from 3.2–4.4% in six replication studies providing this information. Because results from our largest unselected community-based cohort (Framingham) were on the lower bound of these estimates (3.2%), we felt reassured that the winner's curse is not a major concern in this instance, and selected it to estimate the proportion of heritability explained and the genotype score. With a heritability estimate of 30.4% in Framingham, these 14 loci explain a substantial proportion (~10%) of the inherited variation in FG. If these same loci harbor additional independent variants (e.g. those due to low frequency alleles not captured by this analysis) that also influence FG27, this estimate of the heritability attributable to these loci is likely to be conservative.

We estimated the combined impact of the 16 loci associated with FG (the 14 loci included in the genotype score plus *TCF7L2* and *SLC30A8*) in some of the largest cohorts (Framingham, NFBC 1966 and ARIC) by constructing a genotype score equal to the sum of the expected number of risk alleles at each SNP weighted by their effect sizes (see Online Methods). FG levels were higher in individuals with higher genotype scores (Figure 3), with mean differences of ~0.4 mmol/L (5.93 vs 5.51 mmol/L in NFBC 1966; 5.36 vs 5.03 mmol/L in Framingham; 5.70 vs 5.29 mmol/L in ARIC) comparing individuals with a score of 23 or higher (5.6% of the sample) to those with a genotype score of 12 or lower (2.9% of the sample). The 0.4 mmol/L (7.2 mg/dl) difference between the two tails of the distribution of risk score in the population (top 5.6% vs bottom 2.9%) is of clinical relevance, as it represents a shift of approximately 25 centile points in the distribution of FG. Prospective evidence has shown that a difference of this magnitude in FG is associated with a relative risk of 1.54–1.73 for future T2D, accounting for other risk factors28. The impact of individual SNPs on FG in the combined discovery and replication samples is shown in Supplementary Figure 3a–p.

We also analyzed data from 1,602 white European children aged 5.9–17.2 from two studies. Though directionally consistent with observations in adults, some effect size estimates were of smaller magnitude (data not shown). As in adults, the largest effect sizes were observed for risk alleles in *GCK* (beta=0.085; P=1.2×10^{-5}; N=1,602), *G6PC2* (beta=0.062; P=1.9×10^{-4}; N=1,582) and *MTNR1B* (beta=0.033; P=0.058; N=1,309).

Impact of reproducibly associated loci on additional glycemic traits

We sought to investigate all 17 loci associated with FG/HOMA-B or FI/HOMA-IR at genome-wide significance for their effects on other continuous glycemic traits. While most of the 16 loci associated with FG are also strongly associated with HOMA-B (Tables 1 and 2), the associations between FG loci and FI were at best weak; *GCKR* is the only locus reaching genome-wide significant associations for both FG/HOMA-B and FI/HOMA-IR, with the glucose-raising C allele being associated with increased FI (global P=3.6×10^{-20}) and HOMA-IR (global P=3.0×10^{-24}). These patterns are consistent with the gross trait correlations obtained in Framingham for FG and HOMA-B (r=−0.43) and for FG and FI (r=0.25).

Impairment of glucose homeostasis may be characterized by elevated FG or FI, elevated 2-hour glucose or 2-hour insulin post-oral glucose tolerance test (OGTT), or elevated glycated

hemoglobin (HbA_{1c}). We tested associations of each of the 17 loci in a subset of MAGIC cohorts with GWAS data informative for these traits. Since HbA_{1c} is a measure of average glycemia over the preceding 2–3 months, we hypothesized that if an association with additional traits was present it should be directionally consistent. The three loci with the largest effect sizes on FG (*G6PC2*, *MTNR1B* and *GCK*) all showed genome-wide significant and directionally consistent associations with HbA_{1c}, with *DGKB/TMEM195*, *ADCY5*, *SLC2A2*, *PROX1*, *SLC30A8* and *TCF7L2* showing nominal (P<0.05) evidence of directionally consistent association (Table 2). The FG-raising alleles at *TCF7L2*, *SLC30A8*, *GCK* and *ADCY5* were associated (P<0.0002) with increased 2-hour glucose (Table 2); a parallel MAGIC project reports the genome-wide significant association with 2-hour glucose of another *ADCY5* SNP in strong linkage disequilibrium (LD) with our lead SNP (r^2=0.82)29. Consistent with previous reports that the FG-raising allele is associated with greater insulin release during OGTT11,12,30, the FG-raising allele in *GCKR* was associated with lower 2-hour glucose.

Testing of these loci for association with T2D as a dichotomous trait in up to 40,655 cases and 87,022 non-diabetic controls demonstrated that the FG-raising alleles at seven loci (*ADCY5*, *PROX1*, *GCK*, *GCKR* and *DGKB/TMEM195* and the known T2D genes *TCF7L2* and *SLC30A8*), are robustly associated (P<5×10^{-8}) with increased risk of T2D (Table 2); the association of a highly correlated SNP in *ADCY5* with T2D in partially overlapping samples is reported by our companion manuscript29. We found less significant T2D associations (P<5×10^{-3}) for variants in or near *CRY2*, *FADS1*, *GLIS3* and *FAM148B* (Table 2). These data clearly show that loci with very similar FG effect sizes may have very different T2D risk effects (see for example *ADCY5* and *MADD* in Table 2).

Given that several alleles associated with higher FG levels were also associated with increased T2D risk and that the T2D genes *TCF7L2* and *SLC30A*8 showed association with FG, we systematically investigated association of all established T2D loci with the same four fasting diabetes-related quantitative traits. We found directionally consistent nominal associations (P<0.05) of T2D risk alleles with higher FG for 11 of 18 established T2D loci, including *MTNR1B* (Supplementary Table 3). These data demonstrate that a large T2D effect size does not always translate to an equivalently large FG effect in non-diabetic persons, as clearly highlighted when contrasting the remarkably small effects of *TCF7L2* on FG compared to *MTNR1B* (Table 2).

Impact of reproducibly associated loci on additional metabolic traits

Next, we used available GWAS results for additional metabolic phenotypes (BMI from GIANT31, blood pressure from Global BPGen32, and lipids from ENGAGE33), to assess the impact of the newly discovered glycemic loci on these traits. None of the novel loci had significant (P<0.01) associations with BMI or blood pressure (Table 3). Interestingly, the *FADS1* glucose-raising allele was associated with increased total cholesterol (P=2.5×10^{-6}), low-density lipoprotein cholesterol (P=8.5×10^{-6}) and high-density lipoprotein cholesterol (P=2.9×10^{-5}), but lower triglyceride levels (P=1.9×10^{-6}) (Table 3); a consistent association of this locus with lipid levels has been previously reported34. The FG-associated variant in *MADD* was not associated with lipid levels and is not in LD (r^2<0.1) with a previously reported high-density lipoprotein cholesterol SNP (rs7395662)33, suggesting two independent signals within the same locus, one affecting lipid levels and the other FG levels (Table 3).

Potential functional roles of novel associated loci

We investigated the likely functional role of genes mapping closest to the lead SNPs using several sources of data, including human disease databases, evidence from animal models

and bioinformatic analyses (see Box, Online Methods and Supplementary Table 4). The newly discovered and established glycemic loci represent various biological functions: signal transduction (*DGKB/TMEM195, ADCY5, FADS1, ADRA2A, SLC2A2, GCK, GCKR, G6PC2, IGF1*); cell proliferation and development (*GLIS3, MADD, PROX1*); glucose transport and sensing (*SLC2A2, GCK, GCKR, G6PC2*); and circadian rhythm regulation (*MTNR1B, CRY2*). All of these pathways represent further avenues for physiological characterization and possible therapeutic intervention. However, we note that other genes could be causal (Box and Supplementary Table 4) and further experimental evidence will be needed to link unequivocally specific genes with phenotypes.

Expression analyses

We measured expression of the genes mapping closest to our lead SNPs (in *DGKB/TMEM195, ADCY5*, *MADD*, its neighboring gene *SLC39A13* [a member of a family of zinc transporters mapping ~45 kb from the *MADD* lead SNP], *ADRA2A*, *FADS1, CRY2*, *SLC2A2*, *GLIS3*, *PROX1* and *FAM148B*) in human pancreas and other metabolically relevant tissues (Supplementary Figure 4a). While there was evidence of expression in human islets for nearly all genes tested (with the sole exception of *TMEM195*), we found that *DGKB* and *MADD* were most strongly expressed in brain, *SLC2A2*, *FADS1*, *TMEM195* and *PROX1* in liver and *ADCY5* in heart, while *SLC39A13*, *ADRA2A* and *CRY2* were broadly expressed. Strikingly, *FAM148B* was highly expressed in the whole pancreas with lower levels in isolated islets, suggesting that it is also present in exocrine cells. A duplicate experiment in a different laboratory obtained similar results (Supplementary Figure 4b). We further examined expression of these transcripts in flow-sorted human β-cells from two separate individuals and documented β-cell expression for all but *TMEM195,* with *SLC39A13*, *CRY2*, *GLIS3* and *PROX1* being particularly highly expressed in these cells (Supplementary Figure 4c). Expression levels in metabolically relevant tissues for *DGKB* (β cells) and *TMEM195* (liver) provide equally credible evidence for their respective candidacies as the causal gene at these loci. Furthermore, based on its relatively high expression levels in the β cell, *SLC39A13* (neighboring gene to *MADD*) constitutes an intriguing candidate gene that may merit further investigation.

Potential causal variants, eQTLs and copy number variants

Our results interrogate only a fraction of the common variants in any given genomic region; we therefore expect that for the majority of the loci here described the underlying causal variant has yet to be identified. Nevertheless for some there are intriguing possible SNP candidates: in *SLC2A2* the lead SNP (rs11920090) is in perfect LD ($r^2 = 1.0$) with rs5400 (Stage 1 discovery association $P=5.9\times10^{-6}$), which codes for the amino acid substitution T110I, predicted to be “possibly damaging” by PolyPhen35 and PANTHER (Pdel= 0.92)36. In *GCKR* the lead SNP is in strong LD ($r^2=0.93$) with rs1260326, encoding P446L, a non-synomymous variant previously associated with the same traits30 and predicted by PolyPhen to be “probably damaging”. A recent functional study has demonstrated that this variant indirectly leads to increased GCK activity, resulting in the observed effects on FG and triglyceride levels37. Both *SLC2A2* T110I and *GCKR* P446L were predicted “tolerated” by SIFT38, highlighting the difficulties in obtaining consensus functional predictions from different informatic approaches.

We used publicly available eQTL datasets for liver39, cortex40 and Epstein-Barr virus-transformed lymphoblastoid cell lines41 to explore additional possible causal mechanisms testing for association between replicated loci and mRNA expression levels of nearby genes (Online Methods). The lead SNP in *FADS1*, rs174550, is in strong LD ($r^2=0.80$) and close proximity (130 bp) to rs174548, a SNP highly associated with *FADS1* mRNA expression levels in liver ($P=1.7\times10^{-5}$) and with *FADS2* mRNA expression levels in lymphoblastoid

cells (P=3.1×10^{-4}). SNP rs174548 has also been associated (up to P=4.5×10^{-8}) with a number of serum glycerophospholipid concentrations in a GWAS investigating metabolomic profiles42 and rs174550 also demonstrated strong associations (P<5.2×10^{-7}) with the same metabolites (data not shown). These results are substantiated by previous work associating SNPs in this region with the fatty acid composition of phospholipids43. The latter suggest the minor allele variant of rs174550 results in a reduced efficiency of the fatty acid delta-5 desaturase reaction42. Finally, bioinformatic analysis identifies a perfect proxy, rs174545 (r^2=1 with rs174550), whose glucose-raising allele abolishes a predicted miR-124 target site (see Online Methods). Taken together, these data support the hypothesis that not only fatty acid levels, but also their precise composition and degree of desaturation, may influence glucose homeostasis.

Although our study was not designed to explicitly investigate the impact of copy number variation on glycemic traits, we took advantage of existing data44 to investigate whether any of our lead SNPs are in LD with common, diallelic copy number polymorphisms (CNPs) mapping within a 1Mb window. Of the FG loci, only *DGKB/TMEM195* has a validated, common CNP affecting sequence within 1 Mb of the index SNP44. Despite the proximity of this CNP to the associated SNP (~25 kb), the CNP is essentially uncorrelated with the index SNP (r^2=0.01 in HapMap CEU) and is therefore unlikely to explain the observed FG association.

DISCUSSION

In this meta-analysis of 21 Stage 1 discovery GWAS cohorts followed by targeted Stage 2 replication of 25 loci in 33 additional cohorts (totaling up to 122,743 non-diabetic participants), we report the novel genome-wide significant associations of SNPs in or near *ADCY5*, *MADD*, *ADRA2A*, *CRY2*, *FADS1*, *GLIS3*, *SLC2A2*, *PROX1* and *FAM148B* with FG and one SNP near *IGF1* with FI and HOMA-IR. We have also confirmed associations of variants in *GCK*, *GCKR*, *G6PC2* and *MTNR1B* with FG, and achieved genome-wide significance for the recently reported *DGKB/TMEM195* locus24 and for variants in the known T2D-associated *TCF7L2* and *SLC30A8*. All of the FG-associated SNPs demonstrate consistent nominal associations with HOMA-B; and those in *GCK*, *G6PC2*, *MTNR1B*, *DGKB/TMEM195*, *ADCY5*, *FADS1* and *GLIS3* do so at genome-wide significant levels. As previously reported11,12,30, *GCKR* is also associated with FI and HOMA-IR.

Importantly, in addition to the established T2D-associated loci *TCF7L2*, *SLC30A8* and *MTNR1B*, five of the loci that are associated with elevated FG levels in non-diabetic individuals (*ADCY5*, *GCK*, *GCKR*, *PROX1* and *DGKB/TMEM195*) also increase the risk of T2D in separate T2D case-control studies. However, this overlap is incomplete and highlights that the magnitude of the effect on FG is not predictive of the effect on T2D risk, as shown when comparing FG and T2D effect sizes for *MTNR1B* and *TCF7L2*, or for *ADCY5* and *MADD* (Table 2). The latter two loci have similar effect sizes on FG and similar allele frequencies, and yet the former is robustly associated with T2D risk (OR 1.12, P=5.5×10^{-21}) while the latter is not (OR 1.01, P=0.3) in the same samples. This suggests that not all loci associated with FG within the "physiological" range are also associated with "pathological" FG levels and T2D risk. Thus, variation in FG in healthy individuals is not necessarily an endophenotype for T2D, which posits the hypothesis that the mechanism by which glucose is raised, rather than a mere elevation in fasting glucose levels, is a key contributor to disease progression. On the other hand, we cannot rule out the existence of protective variants in loci where elevated FG does not progress to manifest T2D, or the effect of cohort selection in the detection of the loci with variable effects on FG and T2D

risk. Nevertheless, this work shows that targeting quantitative traits in GWAS searches can help identify genetic determinants of overt disease.

With regard to insulin resistance, our analyses resulted in only one novel genome-wide significant locus associated with FI and HOMA-IR. The associated SNP rs35767 is 1.2 kb upstream of *IGF1*, raising the possibility that it may influence IGF1 expression levels (we have found no direct support for this notion in the limited eQTL data available). Although not reaching genome-wide-significance, we note that SNP rs4675095 in the insulin receptor substrate-1 gene (*IRS1*) was also associated with HOMA-IR (P=4.6×10^{-3}), which given *IRS1*'s excellent biological credentials will warrant further investigation. This SNP is not in LD with the widely studied missense SNP G972R (rs1801278) nor with the newly discovered T2D SNP rs294364145, whose C risk allele was only nominally associated with increased FI (P=0.02) and HOMA-IR (P=0.04) in our discovery dataset. The previously reported associations of SNPs in *PANK1* with fasting insulin24 did not receive strong support in our discovery cohorts (P=0.04 and 0.17 for rs11185790 and rs1075374, respectively).

Notably, our large-scale meta-analyses produced more than a dozen robust associations with FG and only two with FI/HOMA-IR (*GCKR* and *IGF1*). Although the somewhat smaller sample size for insulin may have contributed to this discrepancy, a comparison of the similarly-powered HOMA-B and HOMA-IR analyses reveals associations with HOMA-B several orders of magnitude more significant than those seen with HOMA-IR (Figure 2). Because insulin itself is a component of the numerator in both measures, one cannot attribute this discrepancy to technical differences in insulin measurements across cohorts. Similarly, because the QQ plots are very similar for FI and HOMA-IR, we do not believe that the use of a mathematical formula (HOMA-IR) rather than a direct measurement (FI) has affected our analyses substantially. HOMA-B and HOMA-IR have comparable heritability estimates (0.26 and 0.27 in Framingham respectively) and their correlation is significant (r=0.55 in Framingham). Thus, not only there may be a difference in the identity of specific genetic determinants for each trait46, but rather the genetic architecture may be distinct for each trait, with more modest effects, fewer loci, rarer variants or a stronger environmental modification underlying HOMA-IR. In addition, HOMA-IR (which is composed of fasting values) is an imperfect estimate of global insulin resistance, as it addresses mostly hepatic sensitivity to insulin and is partially affected by β-cell function: its heritability is lower than insulin sensitivity derived from the minimal model47. Exploration of gene × environment interactions and analysis of datasets that include 2-hour glucose and insulin values may reveal other genetic factors that increase insulin resistance in humans29.

In conclusion, a large-scale meta-analysis of GWAS has identified ten novel loci associated with glycemic traits whose in-depth physiological investigation should further our understanding of glucose homeostasis in humans and may reveal novel pathways for diabetes therapeutics.

BOX: GENES NEAREST TO LOCI ASSOCIATED WITH FASTING DIABETES-RELATED QUANTITATIVE TRAITS

DGKB/TMEM195 – This locus was recently reported to be associated with FG24; here we report genome-wide significant replication of that finding and evaluate the genes mapping closest to the lead SNP in further detail. *DGKB* encodes the β (1 of 10) isotype of the catalytic domain of diacylglycerol kinase, which regulates the intracellular concentration of the second messenger diacylglycerol. In rat pancreatic islets glucose increases diacylglycerol49, which activates protein kinase C (PKC) and thus potentiates

insulin secretion50. *TMEM195* encodes transmembrane protein 195, an integral membrane phosphoprotein highly expressed in liver.

ADCY5 encodes adenylate cyclase 5, which catalyzes the generation of cAMP. Upon binding to its receptor in pancreatic β cells, glucagon-like peptide 1 (GLP-1) induces cAMP-mediated activation of protein kinase A, transcription of the proinsulin gene and stimulation of insulin secretory processes51.

MADD encodes mitogen-activated protein kinase (MAPK) activating death domain, an adaptor protein that interacts with the tumor necrosis factor α receptor to activate MAPK. Both PKC and MAPK have been implicated in the proliferation of β cells induced by GLP-151, suggesting that *DGKB* and *MADD* may contribute to β-cell mass and insulin secretion in this manner as well. Also in this region, *SLC39A13* encodes a putative zinc transporter required for connective tissue development and BMP/TGF-β signaling52. *NR1H3* encodes the liver X receptor alpha (LXRA) protein, which contains the retinoid response element. Glucose stimulates the transcriptional activity of LXR, which acts as a molecular switch that integrates hepatic glucose metabolism and fatty acid synthesis53.

ADRA2A encodes the α_{2A} adrenergic receptor, which is expressed in β cells and whose activation leads to an outward potassium current independent of the islet K_{ATP} channel, thus possibly modifying insulin release54. Mice with null mutations display abnormal glucose homeostasis in addition to cardiac hypertrophy and abnormal heart rate and blood pressure.

FADS1 encodes fatty acid desaturase 1, which catalyzes the biosynthesis of highly unsaturated fatty acids from precursor essential polyunsaturated fatty acids. One such product is arachidonic acid; in rodent β cells, arachidonic acid liberated by phospholipase A_2 augments glucose-mediated insulin release55. Two other members of the same family, *FADS2* and *FADS3*, also reside in this region. By directing fatty acids down this metabolic pathway, increased activity of these enzymes may lower circulating triglyceride concentrations.

CRY2 encodes cryptochrome 2, an integral component of the mammalian circadian pacemaker56. Mice with null mutations in this gene present with abnormal circadian rhythmicity and several metabolic abnormalities including impaired glucose tolerance, increased insulin sensitivity, decreased body weight and adipose tissue, and abnormal heart rate. Together with *MTNR1B*15¯17 this is the second circadian gene associated with FG in humans, contributing further evidence to this emerging pathway regulating glucose homeostasis57. In the same region, *MAPK8IP1* encodes the scaffolding protein JIP1. Cross-talk between JIP1 and JIP3 has been implicated in the regulation of ASK1-SEK1-JNK signaling during glucose deprivation58. A missense mutation in this gene (S59N) segregates with diabetes in one family affected with a Mendelian form of the disease59.

SLC2A2 encodes the GLUT2 transporter responsible for transport of glucose into β cells and triggering the glucose-mediated insulin secretion cascade. In humans, recessive mutations in this gene lead to Fanconi-Bickel Syndrome, a rare disorder characterized by hepatorenal glycogen accumulation, proximal renal tubular dysfunction and impaired utilization of glucose and galactose60; mouse mutants also display hyperglycemia and abnormal glucose homeostasis61.

GLIS3 encodes the transcription factor GLIS family zinc finger 3 isoform, a Krüppel-like zinc finger protein that both activates and represses transcription and participates in β-cell ontogeny62,63. Functional mutations in this gene cause a syndrome of neonatal diabetes and congenital hypothyroidism63. Polymorphisms within this gene have recently been associated with type 1 diabetes risk (t1dgc.org).

PROX1 encodes the prospero homeobox protein 1, a novel co-repressor of hepatocyte nuclear factor 4α64 that plays a crucial role in β-cell development; mutations in its target gene *HNF4A* cause maturity-onset diabetes of the young, type 165.

FAM148B encodes the nuclear localized factor 2 (NLF2). It is expressed in endothelial cells and up-regulated by pro-inflammatory cytokines66. As shown here, it has a high level of expression in the pancreas, although its putative molecular connection with glucose homeostasis is presently unclear.

IGF1 encodes the insulin-like growth factor 1, the sole genome-wide significant locus associated with HOMA-IR in our study. Humans and mice null for igf1 display abnormal glucose homeostasis, with insulin resistance, increased circulating insulin and insensitivity to growth hormone67.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. American Diabetes Association. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care. 2003; 26:3160–3167. [PubMed: 14578255]
2. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999; 22:233–240. [PubMed: 10333939]
3. Meigs JB, Nathan DM, D'Agostino RB Sr, Wilson PW. Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care. 2002; 25:1845–1850. [PubMed: 12351489]
4. UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352:837–853. [PubMed: 9742976]
5. Patel A, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008; 358:2560–2572. [PubMed: 18539916]
6. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359:1577–1589. [PubMed: 18784090]
7. Ray KK, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009; 373:1765–1772. [PubMed: 19465231]
8. Prokopenko I, McCarthy MI, Lindgren CM. Type 2 diabetes: new genes, new understanding. Trends in Genetics. 2008; 24:613–621. [PubMed: 18952314]
9. Florez JC. Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: Where are the insulin resistance genes? Diabetologia. 2008; 51:1100–1110. [PubMed: 18504548]
10. Weedon MN, et al. A common haplotype of the glucokinase gene alters fasting glucose and birth weight: association in six studies and population-genetics analyses. Am J Hum Genet. 2006; 79:991–1001. [PubMed: 17186458]
11. Sparso T, et al. The GCKR rs780094 polymorphism is associated with elevated fasting serum triacylglycerol, reduced fasting and OGTT-related insulinaemia, and reduced risk of type 2 diabetes. Diabetologia. 2008; 51:70–75. [PubMed: 18008060]
12. Orho-Melander M, et al. A common missense variant in the glucokinase regulatory protein gene (*GCKR*) is associated with increased plasma triglyceride and C-reactive protein but lower fasting glucose concentrations. Diabetes. 2008; 57:3112–3121. [PubMed: 18678614]
13. Bouatia-Naji N, et al. A polymorphism within the *G6PC2* gene is associated with fasting plasma glucose levels. Science. 2008; 320:1085–1088. [PubMed: 18451265]

14. Chen W-M, et al. Association studies in Caucasians identify variants in the *G6PC2/ABCB11* region regulating fasting glucose levels. J Clin Invest. 2008; 118:2620–2628. [PubMed: 18521185]
15. Prokopenko I, et al. Variants in *MTNR1B* influence fasting glucose levels. Nat Genet. 2009; 41:77–81. [PubMed: 19060907]
16. Lyssenko V, et al. Common variant in *MTNR1B* associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat Genet. 2009; 41:82–88. [PubMed: 19060908]
17. Bouatia-Naji N, et al. A variant near *MTNR1B* is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet. 2009; 41:89–94. [PubMed: 19060909]
18. Matthews DR, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Diabetologia. 1985; 28:412–419. [PubMed: 3899825]
19. Pe'er I, Yelensky R, Altshuler D, Daly MJ. Estimation of the multiple testing burden for genomewide association studies of nearly all common variants. Genet Epidemiol. 2008; 32:381–385. [PubMed: 18348202]
20. Brunzell JD, et al. Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. J Clin Endocrinol Metab. 1976; 42:222–229. [PubMed: 1262429]
21. Weir GC, Bonner-Weir S. Five stages of evolving b-cell dysfunction during progression to diabetes. Diabetes. 2004; 53:S16–S21. [PubMed: 15561905]
22. Marchini J, Howie B, Myers S, McVean G, Donnelly P. A new multipoint method for genome-wide association studies by imputation of genotypes. Nat Genet. 2007; 39:906–913. [PubMed: 17572673]
23. Li Y, Abecasis GR. Mach 1.0: Rapid haplotype reconstruction and missing genotype inference. Am J Hum Genet. 2006; S79:2290.
24. Sabatti C, et al. Genome-wide association analysis of metabolic traits in a birth cohort from a founder population. Nat Genet. 2009; 41:35–46. [PubMed: 19060910]
25. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University and Novartis Institutes for BioMedical Research. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science. 2007; 316:1331–1336. [PubMed: 17463246]
26. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. Nat Genet. 2001; 29:306–309. [PubMed: 11600885]
27. Nejentsev S, Walker N, Riches D, Egholm M, Todd JA. Rare variants of *IFIH1*, a gene implicated in antiviral responses, protect against type 1 diabetes. Science. 2009
28. Tirosh A, et al. Normal fasting plasma glucose levels and type 2 diabetes in young men. N Engl J Med. 2005; 353:1454–1462. [PubMed: 16207847]
29. Saxena R, et al. Genetic variation in gastric inhibitory polypeptide receptor (*GIPR*) impacts the glucose and insulin responses to an oral glucose challenge. Nat Genet. (submitted).
30. Vaxillaire M, et al. The common P446L polymorphism in *GCKR* inversely modulates fasting glucose and triglyceride levels and reduces type 2 diabetes risk in the DESIR prospective general French population. Diabetes. 2008; 57:2253–2257. [PubMed: 18556336]
31. Willer CJ, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. Nat Genet. 2009; 41:25–34. [PubMed: 19079261]
32. Newton-Cheh C, et al. Eight blood pressure loci identified by genomewide association study of 34,433 people of European ancestry. Nature Genetics. 2009 online [Epub ahead of print].
33. Aulchenko YS, et al. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. Nat Genet. 2009; 41:47–55. [PubMed: 19060911]
34. Kathiresan S, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet. 2009; 41:56–65. [PubMed: 19060906]
35. Sunyaev S, et al. Prediction of deleterious human alleles. Hum Mol Genet. 2001; 10:591–597. [PubMed: 11230178]
36. Thomas PD, et al. Applications for protein sequence-function evolution data: mRNA/protein expression analysis and coding SNP scoring tools. Nucleic Acids Res. 2006; 34:W645–W650. [PubMed: 16912992]

37. Beer NL, et al. The P446L variant in *GCKR* associated with fasting plasma glucose and triglyceride levels exerts its effect through increased glucokinase activity in liver. Hum Mol Genet. 2009 online [Epub ahead of print].
38. Ng PC, Henikoff S. Predicting deleterious amino acid substitutions. Genome Res. 2001; 11:863–874. [PubMed: 11337480]
39. Schadt EE, et al. Mapping the genetic architecture of gene expression in human liver. PLoS Biology. 2008; 6:e107. [PubMed: 18462017]
40. Myers AJ, et al. A survey of genetic human cortical gene expression. Nat Genet. 2007; 39:1494–1499. [PubMed: 17982457]
41. Dixon AL, et al. A genome-wide association study of global gene expression. Nat Genet. 2007; 39:1202–1207. [PubMed: 17873877]
42. Gieger C, et al. Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. PLoS Genet. 2008; 4:e1000282. [PubMed: 19043545]
43. Schaeffer L, et al. Common genetic variants of the *FADS1 FADS2* gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Hum. Mol. Genet. 2006; 15:1745–1756. [PubMed: 16670158]
44. McCarroll SA, et al. Integrated detection and population-genetic analysis of SNPs and copy number variation. Nat Genet. 2008; 40:1166–1174. [PubMed: 18776908]
45. Rung J, et al. Genetic variant near *IRS1* is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nat Genet. 2009 online [Epub ahead of print].
46. Doria A, Patti M-E, Kahn CR. The emerging genetic architecture of type 2 diabetes. Cell Metabolism. 2008; 8:186–200. [PubMed: 18762020]
47. Bergman RN, et al. Minimal model-based insulin sensitivity has greater heritability and a different genetic basis than homeostasis model assessment or fasting insulin. Diabetes. 2003; 52:2168–2174. [PubMed: 12882937]
48. Higgins JP, Thompson SG. Quantifying heterogeneity in a metaanalysis. Stat Med. 2002; 21:1539–1558. [PubMed: 12111919]
49. Peter-Riesch B, Fathi M, Schlegel W, Wollheim CB. Glucose and carbachol generate 1,2-diacylglycerols by different mechanisms in pancreatic islets. J Clin Invest. 1988; 81:1154–1161. [PubMed: 2832445]
50. Prentki M, Matschinsky FM. Ca2+, cAMP, and phospholipid-derived messengers in coupling mechanisms of insulin secretion. Physiol. Rev. 1987; 67:1185–1248. [PubMed: 2825225]
51. Drucker DJ. The role of gut hormones in glucose homeostasis. J Clin Invest. 2007; 117:24–32. [PubMed: 17200703]
52. Fukada T, et al. The zinc transporter SLC39A13/ZIP13 is required for connective tissue development; its involvement in BMP/TGF-beta signaling pathways. PLoS ONE. 2008; 3:e3642. [PubMed: 18985159]
53. Mitro N, et al. The nuclear receptor LXR is a glucose sensor. Nature. 2007; 445:219–223. [PubMed: 17187055]
54. Rorsman P, et al. Activation by adrenaline of a low-conductance G protein-dependent K+ channel in mouse pancreatic B cells. Nature. 1991; 349:77–79. [PubMed: 1898674]
55. Keane D, Newsholme P. Saturated and unsaturated (including arachidonic acid) non-esterified fatty acid modulation of insulin secretion from pancreatic beta-cells. Biochem Soc Trans. 2008; 36:955–958. [PubMed: 18793168]
56. Kume K, et al. mCRY1 and mCRY2 are essential components of the negative limb of the circadian clock feedback loop. Cell. 1999; 98:193–205. [PubMed: 10428031]
57. Rudic RD, et al. BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. PLoS Biology. 2004; 2:e377. [PubMed: 15523558]
58. Song JJ, Lee YJ. Cross-talk between JIP3 and JIP1 during glucose deprivation: SEK1-JNK2 and Akt1 act as mediators. J Biol Chem. 2005; 280:26845–26855. [PubMed: 15911620]
59. Waeber G, et al. The gene MAPK8IP1, encoding islet-brain-1, is a candidate for type 2 diabetes. Nat Genet. 2000; 24:291–295. [PubMed: 10700186]

60. Santer R, et al. Mutations in *GLUT2*, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. Nat Genet. 1997; 17:324–326. [PubMed: 9354798]
61. Guillam MT, et al. Early diabetes and abnormal postnatal pancreatic islet development in mice lacking Glut-2. Nat Genet. 1997; 17:327–330. [PubMed: 9354799]
62. Kim Y-S, Nakanishi G, Lewandoski M, Jetten AM. GLIS3, a novel member of the GLIS subfamily of Kruppel-like zinc finger proteins with repressor and activation functions. Nucl. Acids Res. 2003; 31:5513–5525. [PubMed: 14500813]
63. Senee V, et al. Mutations in *GLIS3* are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. Nat Genet. 2006; 38:682–687. [PubMed: 16715098]
64. Song K-H, Li T, Chiang JYL. A prospero-related homeodomain protein is a novel co-regulator of hepatocyte nuclear factor 4α that regulates the cholesterol 7α-hydroxylase gene. J. Biol. Chem. 2006; 281:10081–10088. [PubMed: 16488887]
65. Yamagata K, et al. Mutations in the hepatocyte nuclear factor-4α gene in maturity-onset diabetes of the young (MODY1). Nature. 1996; 384:458–460. [PubMed: 8945471]
66. Warton K, Foster NC, Gold WA, Stanley KK. A novel gene family induced by acute inflammation in endothelial cells. Gene. 2004; 342:85–95. [PubMed: 15527968]
67. Clemmons DR. Role of insulin-like growth factor in maintaining normal glucose homeostasis. Horm Res. 2004; 62 Suppl 1:77–82. [PubMed: 15761237]
68. Servin B, Stephens M. Imputation-based analysis of association studies: candidate regions and quantitative traits. PLoS Genet. 2007; 3:e114. [PubMed: 17676998]
69. Aulchenko YS, Ripke S, Isaacs A, van Duijn CM. GenABEL: an R library for genome-wide association analysis. Bioinformatics. 2007; 23:1294–1296. [PubMed: 17384015]
70. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2007.
71. Petitti, DB. Statistical methods in meta-analysis. In: Petitti, DB., editor. Meta-analysis, decision analysis, and cost-effectiveness analysis. New York, NY: Oxford University Press; 2000. p. 94-118.
72. Devlin B, Roeder K. Genomic control for association studies. Biometrics. 1999; 55:997–1004. [PubMed: 11315092]
73. Lukowiak B, et al. Identification and purification of functional human beta-cells by a new specific zinc-fluorescent probe. J Histochem Cytochem. 2001; 49:519–528. [PubMed: 11259455]

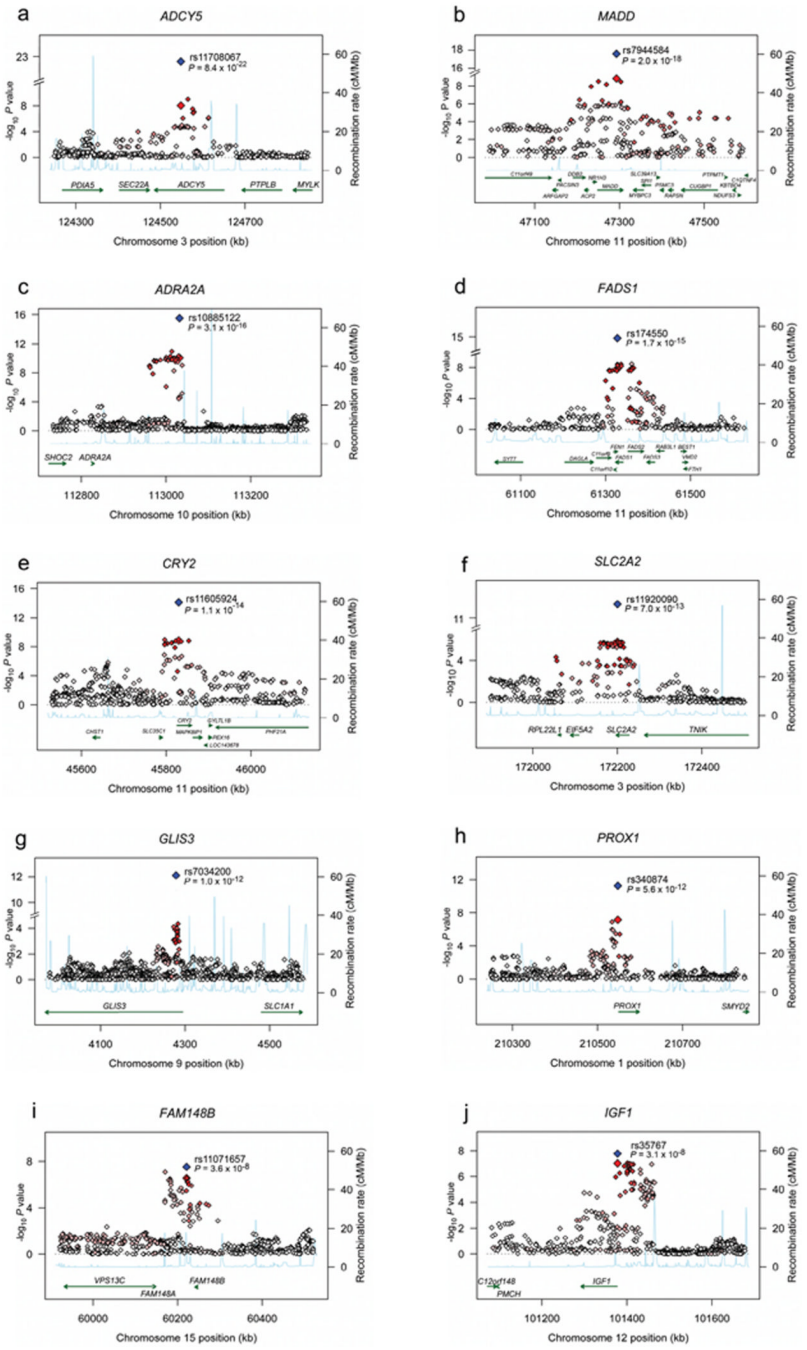

Figure 1.

Regional plots of ten novel genome-wide significant associations. For each of the *ADCY5* (a), *MADD* (b), *ADRA2A* (c), *FADS1* (d), *CRY2* (e), *SLC2A2* (f), *GLIS3* (g), *PROX1* (h), *FAM148B* (i) and *IGF1* (j) regions, directly genotyped and imputed SNPs are plotted with their meta-analysis *P* values (as –log10 values) as a function of genomic position (NCBI Build 35). In each panel, the Stage 1 discovery SNP taken forward to Stage 2 replication is represented by a blue diamond (with global meta-analysis *P* value), with its Stage 1 discovery *P* value denoted by a red diamond. Estimated recombination rates (taken from HapMap) are plotted to reflect the local LD structure around the associated SNPs and their correlated proxies (according to a white to red scale from $r^2 = 0$ to 1, based on pairwise r^2

values from HapMap CEU). Gene annotations were taken from the University of California Santa Cruz genome browser.

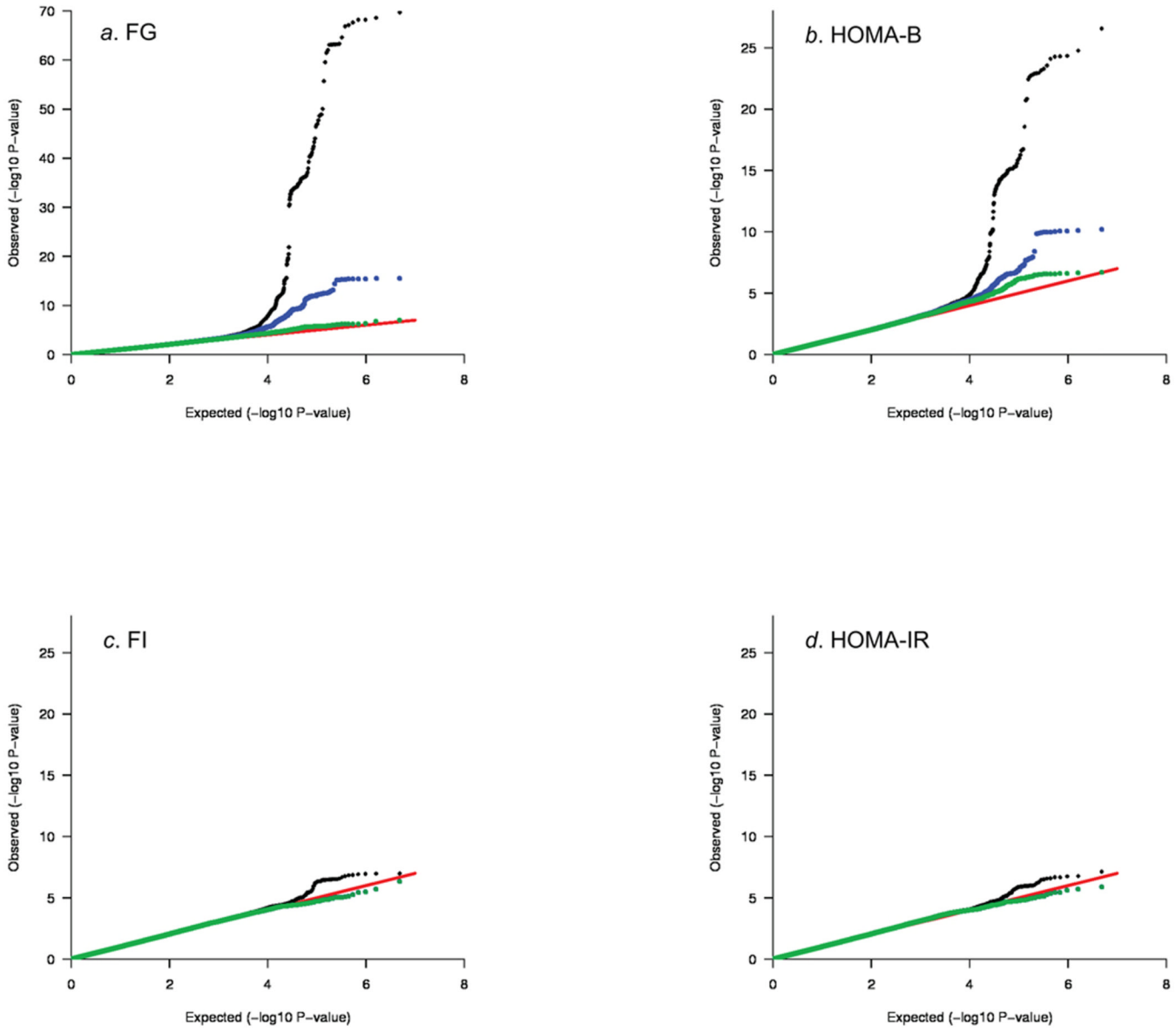

Figure 2.

Quantile-quantile (Q-Q) plots for fasting glucose (FG) (a), β-cell function by homeostasis model assessment (HOMA-B) (b), fasting insulin (FI) (c), and insulin resistance by homeostasis model assessment (HOMA-IR) (d). In each plot, the expected null distribution is plotted along the red diagonal, the entire distribution of observed *P* values is plotted in black, and a distribution that excludes the ten novel findings in Figure 1 is plotted in green. For FG and HOMA-B, the distribution that excludes the four genome-wide significant FG-associated loci (*GCK, GCKR, G6PC2* and *MTNR1B*) is plotted in blue. A comparison of the observed *P* values for each trait shows that FG/HOMA-B associations are much more likely to be detected than FI/HOMA-IR associations.

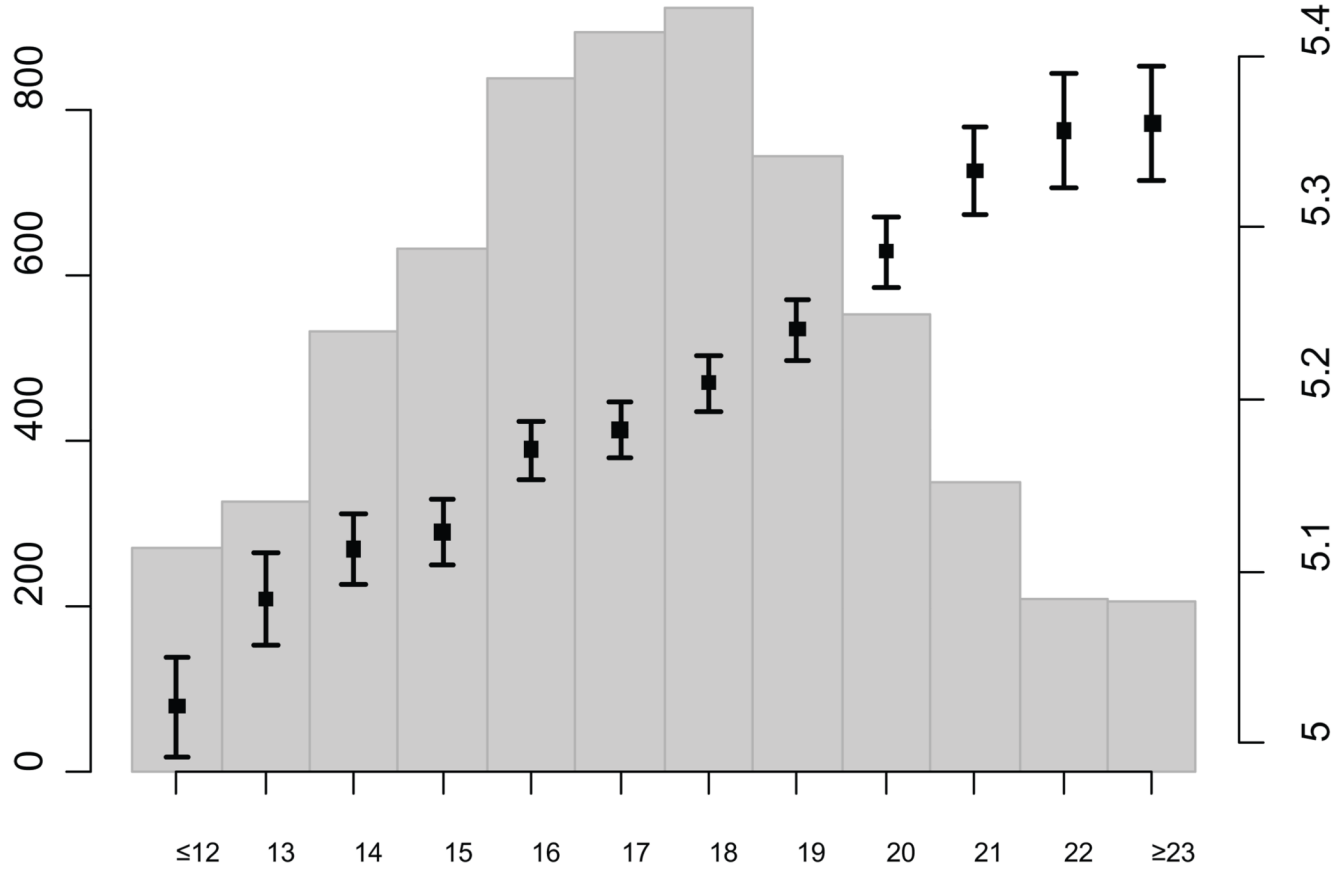

Figure 3.

Variation in levels of fasting glucose depending on the number of risk alleles at novel loci, weighted by effect size in an aggregate genotype score for the Framingham Heart Study. The bar plots show the average and standard error of fasting glucose in mmol/L for each value of the genotype score based on the regression coefficient (right Y axis), and the histogram denotes the number of individuals in each genotype score category (left Y axis). Comparable results were obtained for the NFBC 1966 and ARIC cohorts. On average, the range spans ~0.4 mmol/L (~7.2 mg/dl) from low to high genotype score.

Table 1

SNPs associated with fasting glucose-related or insulin-related traits at genome-wide significance levels

Glucose/HOMA-B selected SNPs				Fasting glucose				HOMA-B			
SNP	**Nearest gene(s)**	**Alleles (effect/ other)**	**Freq**	**Discovery *P* value**	**I^2 estimate (*P* value)**	**Global *P* value**	**Joint analysis N**	**Discovery *P* value**	**I^2 estimate (*P* value)**	**Global *P* value**	**Joint analysis N**
rs560887	*G6PC2*	C/T	0.70	4.4×10^{-75}	0.31 (0.18)	8.7×10^{-218}	119,169	2.0×10^{-28}	0.54 (0.01)	1.5×10^{-66}	94,839
rs10830963	*MTNR1B*	G/C	0.30	1.2×10^{-68}	0.00 (1.00)	5.8×10^{-175}	112,844	1.8×10^{-22}	0.45 (0.03)	2.7×10^{-43}	90,364
rs4607517	*GCK*	A/G	0.16	4.5×10^{-36}	0.19 (0.46)	6.5×10^{-92}	118,500	7.5×10^{-8}	0.36 (0.12)	1.8×10^{-16}	94,112
rs2191349	*DGKB/TMEM195*	T/G	0.52	7.8×10^{-17}	0.10 (0.68)	3.0×10^{-44}	122,743	5.4×10^{-11}	0.09 (0.71)	2.8×10^{-17}	98,372
rs780094	*GCKR*	C/T	0.62	2.5×10^{-12}	0.00 (1.00)	5.6×10^{-38}	118,032	0.25	0.32 (0.18)	3.2×10^{-4}	93,990
rs11708067	*ADCY5*	A/G	0.78	8.7×10^{-9}	0.04 (0.89)	7.1×10^{-22}	118,475	2.2×10^{-4}	0.37 (0.10)	2.5×10^{-12}	94,212
rs7944584	*MADD*	A/T	0.75	1.5×10^{-9}	0.00 (1.00)	2.0×10^{-18}	118,741	1.1×10^{-4}	0.16 (0.51)	3.5×10^{-5}	94,408
rs10885122	*ADRA2A*	G/T	0.87	8.4×10^{-11}	0.00 (1.00)	2.9×10^{-16}	118,410	3.7×10^{-6}	0.11 (0.66)	2.0×10^{-6}	94,128
rs174550	*FADS1*	T/C	0.64	1.5×10^{-8}	0.00 (1.00)	1.7×10^{-15}	118,908	4.5×10^{-5}	0.01 (0.99)	5.2×10^{-13}	94,536
rs11605924	*CRY2*	A/C	0.49	1.5×10^{-9}	0.00 (1.00)	1.0×10^{-14}	116,479	5.2×10^{-6}	0.03 (0.94)	3.2×10^{-5}	92,326
rs11920090	*SLC2A2*	T/A	0.87	1.9×10^{-6}	0.00 (1.00)	8.1×10^{-13}	119,024	1.4×10^{-4}	0.36 (0.11)	4.5×10^{-6}	94,629
rs7034200	*GLIS3*	A/C	0.49	1.2×10^{-4}	0.00 (1.00)	1.0×10^{-12}	106,250	1.9×10^{-6}	0.19 (0.46)	1.2×10^{-13}	83,759
rs340874	*PROX1*	C/T	0.52	7.1×10^{-8}	0.00 (1.00)	6.6×10^{-12}	116,882	3.7×10^{-5}	0.00 (1.00)	5.3×10^{-6}	92,942
rs11071657	*FAM148B*	A/G	0.63	2.8×10^{-7}	0.00 (1.00)	3.6×10^{-8}	114,454	0.23	0.08 (0.73)	0.002	90,675
rs11558471	*SLC30A8*	A/G	0.68	2.6×10^{-11}	-	-	45,996	1.4×10^{-6}	-	-	36,283
rs4506565	*TCF7L2*	T/A	0.31	1.2×10^{-8}	-	-	46,181	1.4×10^{-6}	-	-	36,461
Insulin/HOMA-IR selected SNPs				**Fasting insulin**				**HOMA-IR**			
rs780094	*GCKR*	C/T	0.62	1.1×10^{-4}	0.14 (0.57)	3.6×10^{-20}	96,126	9.9×10^{-7}	0.25 (0.32)	3.0×10^{-24}	94,636
rs35767	*IGF1*	G/A	0.85	1.0×10^{-7}	0.17 (0.50)	3.3×10^{-8}	94,590	7.8×10^{-8}	0.26 (0.28)	2.2×10^{-9}	93,141

Directly genotyped and imputed SNPs were tested for association with fasting glucose, fasting insulin and homeostasis model assessment of β-cell function (HOMA-B) and insulin resistance (HOMA-IR). Twenty one discovery cohorts with genome-wide data were meta-analyzed (Stage 1 discovery) and 25 SNPs were promoted for replication of the same trait in a set of 33 additional cohorts with *in silico* (N=7) or *de novo* (N=26) genotype data (N=31 for fasting insulin, HOMA-B and HOMA-IR; for Stage 2 replication *P*-values and effect sizes see Table 2). A joint analysis was then performed (global). Heterogeneity in the discovery sample was assessed using the I^2 index[48]. Replication was not attempted for SNPs in two known type 2 diabetes genes (*SLC30A8* and *TCF7L2*) which achieved genome-wide significance for FG in Stage 1. Freq denotes the allele frequency of the glucose-raising allele. N=sample size. Note that the previously reported *GCKR* SNP has associations with glucose-related and insulin-related traits.

Table 2

Association of novel SNPs with glycemic traits in MAGIC and type 2 diabetes replication meta-analyses

SNP	Nearest gene(s)	Alleles (effect/ other)		Fasting glucose (mmol/L)	HOMA-B	Fasting insulin (pmol/L)	HOMA-IR	HbA_{1c} (%)	2-hr glucose (mmol/L)	2-hr insulin (pmol/L)	Type 2 diabetes^
rs560887	*G6PC2*	C/T	Effect*	0.075 (0.003)	−0.042 (0.004)	−0.007 (0.004)	0.006 (0.004)	0.032 (0.004)	0.017 (0.020)	−0.031 (0.013)	0.97 (0.95–0.99)
			P-value	8.5×10^{-122}	7.6×10^{-29}	0.11	0.16	1.0×10^{-17}	0.41	0.01	0.012
rs10830963	*MTNR1B*	G/C	Effect*	0.067 (0.003)	−0.034 (0.004)	−0.006 (0.004)	0.004 (0.004)	0.024 (0.004)	0.056 (0.022)	0.034 (0.015)	1.09 (1.06–1.12)
			P-value	1.1×10^{-102}	1.1×10^{-22}	0.14	0.37	3.0×10^{-9}	0.01	0.02	8.0×10^{-13}
rs4607517	*GCK*	A/G	Effect*	0.062 (0.004)	−0.025 (0.005)	0.004 (0.006)	0.015 (0.006)	0.041 (0.005)	0.097 (0.026)	−0.012 (0.015)	1.07 (1.05–1.10)
			P-value	1.2×10^{-44}	1.2×10^{-6}	0.46	0.01	6.3×10^{-19}	2.0×10^{-4}	0.42	5.0×10^{-8}
rs2191349	*DGKB/TMEM195*	T/G	Effect*	0.030 (0.003)	−0.017 (0.003)	−0.002 (0.003)	0.002 (0.004)	0.008 (0.003)	0.000 (0.019)	−0.006 (0.012)	1.06 (1.04–1.08)
			P-value	5.3×10^{-29}	6.4×10^{-8}	0.48	0.61	0.01	0.98	0.60	1.1×10^{-8}
rs780094	*GCKR*	C/T	Effect*	0.029 (0.003)	0.014 (0.003)	0.032 (0.004)	0.035 (0.004)	0.004 (0.004)	−0.091 (0.019)	0.000 (0.011)	1.06 (1.04–1.08)
			P-value	1.7×10^{-24}	1.4×10^{-5}	3.6×10^{-19}	5.0×10^{-20}	0.32	1.4×10^{-6}	1.00	1.3×10^{-9}
rs11708067	*ADCY5*	A/G	Effect*	0.027 (0.003)	−0.023 (0.004)	−0.011 (0.004)	0.006 (0.005)	0.015 (0.004)	0.094 (0.023)	0.008 (0.015)	1.12 (1.09–1.15)
			P-value	1.7×10^{-14}	3.6×10^{-8}	0.01	0.16	5.1×10^{-4}	6.6×10^{-5}	0.60	9.9×10^{-21}
rs7944584	*MADD*	A/T	Effect*	0.021 (0.003)	−0.007 (0.004)	0.002 (0.004)	0.005 (0.004)	0.001 (0.004)	−0.017 (0.022)	−0.019 (0.013)	1.01 (0.99–1.03)
			P-value	5.1×10^{-11}	0.07	0.60	0.26	0.84	0.44	0.15	0.30
rs10885122	*ADRA2A*	G/T	Effect*	0.022 (0.004)	−0.010 (0.005)	0.001 (0.005)	0.004 (0.005)	0.007 (0.005)	0.004 (0.030)	−0.051 (0.019)	1.04 (1.01–1.07)
			P-value	9.7×10^{-8}	0.03	0.90	0.47	0.21	0.89	0.007	0.020
rs174550	*FADS1*	T/C	Effect*	0.017 (0.003)	−0.020 (0.003)	−0.011 (0.004)	0.008 (0.004)	0.007 (0.004)	0.013 (0.019)	−0.003 (0.012)	1.04 (1.02–1.06)
			P-value	8.3×10^{-9}	5.3×10^{-10}	2.7×10^{-3}	0.03	0.053	0.49	0.82	2.3×10^{-4}
rs11605924	*CRY2*	A/C	Effect*	0.015 (0.003)	−0.005 (0.003)	0.001 (0.004)	0.003 (0.004)	0.001 (0.003)	0.023 (0.018)	0.006 (0.011)	1.04 (1.02–1.06)
			P-value	8.1×10^{-8}	0.13	0.73	0.34	0.72	0.20	0.62	1.7×10^{-4}
rs11920090	*SLC2A2*	T/A	Effect*	0.020 (0.004)	−0.012 (0.005)	0.002 (0.005)	0.005 (0.005)	0.017 (0.005)	0.015 (0.027)	−0.022 (0.016)	1.01 (0.99–1.04)
			P-value	3.3×10^{-6}	0.02	0.77	0.37	5.8×10^{-4}	0.58	0.19	0.34
rs7034200	*GLIS3*	A/C	Effect*	0.018 (0.003)	−0.020 (0.004)	−0.014 (0.004)	0.011 (0.004)	0.003 (0.003)	0.037 (0.018)	0.010 (0.011)	1.03 (1.01–1.05)
			P-value	1.2×10^{-9}	8.9×10^{-9}	2.7×10^{-4}	4.6×10^{-3}	0.32	0.04	0.36	1.3×10^{-3}

SNP	Nearest gene(s)	Alleles (effect/ other)		Fasting glucose (mmol/L)	HOMA-B	Fasting insulin (pmol/L)	HOMA-IR	HbA_{1c} (%)	2-hr glucose (mmol/L)	2-hr insulin (pmol/L)	Type 2 diabetes^
rs340874	*PROX1*	C/T	Effect *	0.013 (0.003)	−0.008 (0.003)	−0.002 (0.004)	0.001 (0.004)	0.009 (0.004)	0.030 (0.020)	−0.007 (0.012)	1.07 (1.05–1.09)
			P-value	6.6×10^{-6}	0.02	0.68	0.74	9.5×10^{-3}	0.13	0.56	7.2×10^{-10}
rs11071657	*FAM148B*	A/G	Effect *	0.008 (0.003)	−0.013 (0.004)	−0.009 (0.004)	0.008 (0.004)	0.001 (0.004)	−0.065 (0.020)	−0.006 (0.013)	1.03 (1.01–1.05)
			P-value	0.01	8.1×10^{-4}	0.03	0.07	0.79	0.001	0.65	2.9×10^{-3}
rs13266634	*SLC30A8*	C/T	Effect *	0.027 (0.004)	−0.016 (0.004)	−0.004 (0.005)	0.0002 (0.005)	0.016 (0.004)	0.093 (0.022)	−0.011 (0.015)	1.15 (1.10–1.21)#
			P-value	5.5×10^{-10}	2.4×10^{-5}	0.44	0.97	3.3×10^{-5}	2.0×10^{-5}	0.47	1.5×10^{-8}
rs7903146	*TCF7L2*	T/C	Effect *	0.023 (0.004)	−0.02 (0.004)	−0.012 (0.004)	0.010 (0.005)	0.013 (0.003)	0.118 (0.021)	0.010 (0.013)	1.40 (1.34–1.46)#
			P-value	2.8×10^{-8}	1.4×10^{-7}	0.004	0.03	1.8×10^{-4}	2.6×10^{-8}	0.42	2.2×10^{-51}
rs35767	*IGF1*	G/A	Effect *	0.012 (0.005)	0.009 (0.005)	0.010 (0.006)	0.013 (0.006)	0.010 (0.005)	0.027 (0.025)	0.015 (0.016)	1.04 (1.01–1.07)
			P-value	0.01	0.09	0.10	0.04	0.050	0.28	0.33	6.6×10^{-3}
Sample size for each trait				45,049–76,558	35,435–61,907	37,199–62,264	35,901–62,001	33,718–44,856	15,221–15,234	7,051–7,062	40,655 cases/87,022 controls

* per-allele effect (SE) for quantitative traits was estimated from Stage 2 replication samples for fasting glucose, homeostasis model assessment of β-cell function (HOMA-B), fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR), and from discovery meta-analyses of MAGIC GWAS for glycated hemoglobin (HbA_{1C}), 2-hour glucose after an oral glucose tolerance test (BMI-adjusted) and 2-hour insulin (BMI-adjusted). For the first four traits, the regression coefficients are obtained from the replication cohorts so as to avoid an overestimate of the effect size caused by the "winner's curse". Results from replication samples were unavailable for rs7903146 and rs13266634, thus discovery meta-analysis results are shown for both SNPs for fasting glucose (N=45,049–45,051), HOMA-B (N=35,435–35,437), fasting insulin (N=37,199–37,201) and HOMA-IR (N=35,901–35,903).

Replication genotyping was undertaken in 27 independent type 2 diabetes (T2D) case/control samples for all except the *TCF7L2* and *SLC30A8* signals.

^ Association with T2D for SNPs in *TCF7L2* and *SLC30A8* loci was estimated from the DIAGRAM+ meta-analysis for a total of 8,130 cases/38,987 controls. For these loci we have included data on the most commonly associated SNPs with T2D in previously published data.

Nat Genet. Author manuscript; available in PMC 2011 January 11.

Table 3

Association of novel SNPs with related metabolic traits in other GWAS datasets

SNP	Nearest gene	Alleles (effect/ other)		BMI (kg/m^2)	Diastolic blood pressure (mm Hg)	Systolic blood pressure (mm Hg)	Hypertension	HDL	LDL	Total cholesterol	Triglycerides
rs560887	*G6PC2*	C/T	Effect*	−0.013 (0.010)	−0.146 (0.091)	−0.105 (0.135)	−0.023 (0.028)	−0.004 (0.004)	0.01 (0.011)	0.019 (0.011)	0.004 (0.005)
			P-value	0.18	0.12	0.46	0.41	0.32	0.35	0.10	0.52
rs10830963	*MTNR1B*	G/C	Effect*	0.002 (0.010)	0.034 (0.098)	0.088 (0.146)	−0.003 (0.030)	0.005 (0.004)	−0.015 (0.013)	0.002 (0.014)	−0.004 (0.007)
			P-value	0.86	0.74	0.56	0.91	0.26	0.25	0.88	0.58
rs4607517	*GCK*	A/G	Effect*	0.004 (0.011)	−0.136 (0.111)	−0.128 (0.165)	−0.013 (0.033)	−0.006 (0.005)	0.012 (0.014)	−0.002 (0.015)	0.013 (0.007)
			P-value	0.75	0.23	0.45	0.70	0.21	0.38	0.87	0.054
rs2191349	*DGKB/ TMEM195*	T/G	Effect*	0.001 (0.009)	−0.075 (0.082)	−0.046 (0.122)	0.007 (0.025)	0.002 (0.003)	0.009 (0.01)	0.015 (0.011)	0.004 (0.005)
			P-value	0.95	0.37	0.71	0.79	0.64	0.40	0.18	0.44
rs780094	*GCKR*	C/T	Effect*	0.012 (0.009)	0.052 (0.084)	0.006 (0.124)	0.020 (0.025)	0.009 (0.003)	0.007 (0.01)	−0.019 (0.011)	−0.055 (0.005)
			P-value	0.17	0.55	0.96	0.45	8.7×10^{-3}	0.51	0.08	9.6×10^{-27}
rs11708067	*ADCY5*	A/G	Effect*	−0.010 (0.011)	−0.056 (0.104)	0.047 (0.156)	0.028 (0.031)	0.0004(0.004)	−0.014 (0.013)	−0.013 (0.013)	−0.003 (0.006)
			P-value	0.35	0.60	0.77	0.37	0.92	0.26	0.32	0.62
rs7944584	*MADD*	A/T	Effect*	0.023 (0.010)	−0.208 (0.093)	−0.170 (0.140)	−0.038 (0.028)	0.007 (0.004)	−0.013 (0.012)	−0.016 (0.012)	−0.007 (0.006)
			P-value	0.02	0.03	0.24	0.18	0.06	0.27	0.18	0.26
rs10885122	*ADRA2A*	G/T	Effect*	−0.021 (0.014)	−0.079 (0.131)	0.168 (0.193)	0.073 (0.039)	0.01 (0.007)	−0.019 (0.02)	−0.02 (0.021)	−0.02 (0.01)
			P-value	0.14	0.56	0.40	0.07	0.15	0.34	0.33	0.04
rs174550	*FADS1*	T/C	Effect*	0.003 (0.009)	−0.208 (0.086)	−0.108 (0.128)	0.013 (0.026)	0.014 (0.003)	0.046 (0.010)	0.052 (0.011)	−0.025 (0.005)
			P-value	0.73	0.02	0.42	0.62	2.9×10^{-5}	8.5×10^{-6}	2.5×10^{-6}	1.9×10^{-6}
rs11605924	*CRY2*	A/C	Effect*	0.011 (0.009)	0.123 (0.082)	−0.003 (0.123)	0.004 (0.025)	0.005 (0.004)	0.005 (0.011)	0.008 (0.011)	−0.009 (0.005)
			P-value	0.21	0.15	0.98	0.87	0.13	0.62	0.46	0.10
rs11920090	*SLC2A2*	T/A	Effect*	0.010 (0.012)	−0.034 (0.117)	−0.023 (0.174)	−0.030 (0.036)	0.003 (0.005)	−0.004 (0.014)	−0.009 (0.015)	−0.015 (0.007)
			P-value	0.42	0.78	0.90	0.41	0.60	0.81	0.57	0.04
rs7034200	*GLIS3*	A/C	Effect*	−0.002 (0.009)	0.093 (0.082)	0.087 (0.122)	0.006 (0.025)	0.0002(0.003)	0.015 (0.01)	0.028 (0.011)	0.005 (0.005)
			P-value	0.86	0.27	0.49	0.80	0.94	0.15	8.3×10^{-3}	0.37
rs340874	*PROX1*	C/T	Effect*	−0.007 (0.009)	0.113 (0.085)	0.093 (0.127)	0.029 (0.026)	−0.007 (0.003)	0.009 (0.01)	0.003 (0.011)	0.007 (0.005)

SNP	Nearest gene	Alleles (effect/ other)		BMI (kg/m^2)	Diastolic blood pressure (mm Hg)	Systolic blood pressure (mm Hg)	Hypertension	HDL	LDL	Total cholesterol	Triglycerides
			P-value	0.46	0.20	0.48	0.27	0.04	0.39	0.81	0.19
rs11071657	*FAM148B*	A/G	Effect *	−0.006 (0.010)	0.132 (0.091)	−0.007 (0.135)	0.020 (0.028)	−0.004 (0.004)	0.012 (0.011)	0.002 (0.011)	0.006 (0.005)
			P-value	0.54	0.16	0.96	0.49	0.22	0.28	0.86	0.30
rs13266634	*SLC30A8*	C/T	Effect *	−0.026 (0.011)	−0.081 (0.094)	−0.072 (0.139)	0.010 (0.029)	0.003 (0.004)	0.016 (0.011)	0.013 (0.011)	0.005 (0.005)
			P-value	0.01	0.40	0.62	0.74	0.47	0.13	0.24	0.33
			Effect *	−0.033 (0.009)	0.026 (0.091)	0.025 (0.137)	0.003 (0.028)	0.005 (0.004)	0.007 (0.012)	0.007 (0.012)	−0.006 (0.006)
rs7903146	*TCF7L2*	T/C	*P*-value	4.4×10^{-4}	0.78	0.86	0.92	0.22	0.53	0.55	0.31
rs35767	*IGF1*	G/A	Effect *	0.003 (0.012)	−0.102 (0.113)	−0.078 (0.167)	−0.005 (0.034)	0.003 (0.005)	−0.009 (0.015)	−0.012 (0.015)	−0.002 (0.007)
			P-value	0.81	0.38	0.65	0.87	0.556	0.519	0.425	0.839
			N	28,225–32,530	28,591–34,130	28,557–34,135	8145–9553 cases 8175–9749 controls	21,045	17,521	17,529	21,104

* Per-allele effect (SE). Results for BMI, blood pressure traits and lipid levels were kindly provided by the GIANT 31, GlobalBPGen 32 and ENGAGE 33 consortia respectively.